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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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WILLIAM M SMITH
TOWNSENT AND TOWNSEND AND CREW
TWO EMBARCADERO CNETER
8TH FLOOR
SAN FRANCISCO CA 94111-3834

EXAMINER	
WILSON,M	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/889,355	Applicant(s) Engler H. et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-55* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-55 are under consideration in the instant application.

The Information Disclosure Statement has been considered and made of record.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses methods of enhancing gene therapy, particularly the treatment of bladder cancer with p53 or retinoblastoma gene (page 12, line 25) except for claims 7, 16 and 29 which are directed toward delivering a protein. The specification also contemplates methods of enhancing delivery of diagnostic marker genes (page 10, line 14). As the purpose of the specification is to guide the artisan on the making and using of the claimed invention, the artisan reads the claims in light of the teachings in the specification. Thus, the artisan reading the claimed invention in view of the specification regarding using the invention would only determine the use

of the present invention to be for **enhancing** therapy or diagnosis. If the Applicants feels other uses for the method are disclosed in the specification, then the applicants should point to such uses by page and line number. Thus, the field of the invention is a method of enhancing delivery of genes and proteins for the purpose of therapy or diagnosis.

Applicants demonstrates the use of various detergents in delivering adenoviral vector encoding βGal and demonstrated BigCHAP significantly increased expression of βGal after 48 hours and was not toxic (page 24, Table I). The applicants teach that more than 17.5 mM of BigCHAP caused cystitis (page 26, line 6), a concentration of less than $1.3x10^{10}$ PN/ml delivered to the bladder had decreased expression levels (page 26, line 15), different brands of BigCHAP, such as Sigma and Calbiochem (page 28, line 27 and line 30, respectively), provide different results (page 28, line 26), and that impurities in BigCHAP are **essential** to the obtain increased expression (page 30, lines 1-20). In fact, pure BigCHAP fails to enhance gene expression (page 30, lines 1-7). Thus, it is not clear that pure BigCHAP, any commercial brand of BigCHAP with any impurities, or any lot or batch of BigCHAP from one particular company can be used in the method claimed such that delivery is **enhanced**. The specification does not provide guidance as to the impurities or their concentration needed to obtain enhanced delivery. One of skill in the art would not know what impurities are essential for BigCHAP to obtain an increase in gene expression either for a therapeutic or marker use. The specification fails to provide adequate guidance to obtain an increase in gene expression using **any** BigCHAP of **any** lot with **any** impurities.

Examples 8 (page 27, line 7) and 6 (page 25, line 1) demonstrate the expression of p53 and retinoblastoma (RB) genes, respectively, using BigCHAP, but do not determine the level of expression. These and all other examples in the instant application fail to correlate the level of gene expression obtained with a level of expression of p53, RB or any other gene such that a therapeutic effect is obtained much less an **enhanced** expression as disclosed. There is no evidence of the enhanced expression of a therapeutic gene as disclosed in the specification. One of skill in the art would not know what level of expression is required or how long expression of p53 or RB must be maintained to obtain therapeutic value.

At the time of filing, the art was replete with teachings that gene therapy was unpredictable and undeveloped in regard to obtaining therapeutic levels of transcription and /or expression in a host subject without undue experimentation. Eck and Wilson (Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, 1995) disclose that "[w]ith *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc.), as well as for the consequences of altered gene expression and protein function." Eck and Wilson also disclose the conception, yet to be realized, that an ideal gene transfer system would tailor the gene transfer to the specific requirements of the disease being treated (paragraph bridging pages 81-82). Thus, in view of the state of the art of gene therapy, one of skill in the art would have required an undue amount of experimentation to tailor a gene therapy protocol employing a adenoviral sequence encoding a therapeutic molecule to treat a diseases and pathologies disclosed as described in the specification and have a reasonable

expectation of obtaining therapeutic levels of expression of a molecule that would ameliorate symptoms associated with the disease. Verma, et al (Nature, Sept. 18, 1997, page 239-242) states that in gene therapy, "the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, 3rd column, line 10). It is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels; i.e., expression at low levels or at levels providing no patentably useful phenotypic effect; however, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Ross et al. (Human Gene Therapy, Vol. 7, pages 1781-1790, September 1996) suggests no correlation between successful expression of a gene and a therapeutic result (page 1789, column 1, first paragraph). The lack of correlation between expression of a gene product and therapeutic value in the field of gene therapy is exemplified by Marshall (Science, 1995, Vol. 269, pages 1050-1055) as follows: The field of gene therapy is unpredictable and undeveloped because no evidence has been presented demonstrating genetic treatment has therapeutic benefits (page 1050, column 1).

Therefore, in order to claim the benefit of therapy and to have a reasonable expectation of success in obtaining therapeutic levels of expression, the specification is required to provide embodiments or present a clear correlation between the working examples and the claimed method. Thus, where there is a deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product

or protein in an art recognized animal model or patient as claimed. The specification does not provide guidance to overcome these art recognized unpredictabilities of gene therapy because it lacks correlative evidence between administration of a therapeutic gene and a reduction of tumor burden in the bladder or any other therapeutic effect. Nor does the specification provide sufficient evidence that BigCHAP can enhance the expression of a therapeutic gene such that a therapeutic effect can be enhanced. The instant specification fails to provide sufficient guidance to obtain sufficient levels of expression of any gene such that amelioration of symptoms of any disease occurs.

The results obtained using adenoviral vector are not correlated to other vectors such that expression may be obtained for any vector. One of skill would not have a reasonable expectation for success in obtaining successful expression of any gene using any vector.

Claims 7, 16 and 29, directed toward treatment using protein are not enabled because the specification fails to provide sufficient guidance such that one skilled in the art could deliver p53, RB or any other protein such that a therapeutic result is obtained. Because the applicants' claims as written are towards methods of treating disease, specifically bladder cancer, by administering a protein formulated in a buffer comprising a compound claimed without causing **any** phenotypic change to the host, the specification fails to provides sufficient teachings to reach therapeutic results using **any** protein.

Therefore in view of the quantity of experimentation necessary to obtain **enhanced** delivery of proteins or genes or expression of any gene that is of therapeutic value, the lack of

direction and guidance provided by the specification to determine how to use detergents other than BigCHAP, to determine what brand of BigCHAP, what lot number and what impurities are required such that delivery of a molecule is enhanced, the lack of correlation between the expression of a gene to therapeutic levels of expression, of adenoviral vectors to other vectors, the lack of examples demonstrating therapeutic effectiveness or enhancement obtained using the method claimed, and the breath of the claims, the ordinary artisan at the time of the instant invention would not have known how to use the claimed invention without a reasonable expectation of success.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 7, 12, 16, 23, 29 and 41-42, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235).

Claims 1, 7, 12, 16, 23, 29 are drawn to method of therapy or pharmaceutical composition comprising a molecule formulated in a buffer comprising a compound of Formula I. Aungst et al. teach the delivery of insulin with various surfactants including BigCHAP to rats (page 230, Figure 1). Claims 1, 7, 12, 16, 23, 29 are anticipated by Aungst et al. because Aungst et al. delivers a

therapeutic molecule with BigCHAP in the buffer. Claims 41-42 and 45-46 are drawn toward compounds of Formula I which are anticipated by the compound BigCHAP as disclosed in Aungst et al. (page 230, Figure 1). BigCHAP anticipate claims 41-42 and 45 because they contain a cholic acid group and two pentose saccharide groups. Because the applicants' claims as written are towards methods of treating disease, specifically bladder cancer, by administering a protein formulated in a buffer comprising a compound claimed without causing **any** phenotypic change to the host, the cited prior art provides sufficient teachings and motivation to reach mere **delivery** of a protein.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Aungst et al. do not teach the method of administering a gene to a cell comprising the gene formulated in a buffer comprising a compound

of Formula I as described in the claims.

However, at the time of filing Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). It would have been obvious to one of skill at the time the invention was made to combine the surfactants of Aungst et al. with the method of delivering genes with detergents disclosed by Carson et al. Motivation is provided by Carson et al. by stating detergents which facilitate uptake of small molecules are well known in the art and may, without undue experimentation, be adapted for use in facilitating uptake of genes (column 8, line 59). Since the skin is an organ, Carson et al. anticipates claim 6 which limits the tissue to an organ. Because it is obvious for one of skill to vary amounts and to administer enhancing agent with or before administration of a molecule to obtain productive delivery of said molecule, claims 2-4, 13-15, 24-26 and 39-40 are obvious over the prior art. One of skill would have had a reasonable expectation of success in administering a gene to a cell of the skin or mucosa formulated in a buffer comprising BigCHAP or other surfactants. Because the applicants' claims as written are towards methods of treating disease, specifically bladder cancer, by administering a gene formulated in a buffer comprising a compound claimed wherein administration is by **any** route without causing **any** phenotypic change to the host, the cited prior art provides sufficient teachings and motivation to reach mere **delivery** of a gene.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

7. Claims 1, 8-10, 12, 17-19, 23 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) as applied to claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 above, and further in view of Wills et al. (1994, Human gene therapy, Vol. 5, pages 1079-1088).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). It would have been obvious to one of skill at the time the invention was made to combine the surfactants of Aungst et al. with the method of delivering genes with detergents disclosed by Carson et al. Motivation is provided by Carson et al. by stating detergents which facilitate uptake of small molecules are well known in the art and may, without undue experimentation, be adapted for use in facilitating uptake of genes (column 8, line 59). Aungst et al. in view of Carson et al. do not teach the delivery of p53.

However, at the time of filing, Wills et al. disclose the adenovirus encoding p53 for delivery to tumor cells. It would have been obvious to combine the adenovirus encoding p53 with the method of delivering a gene with surfactants as taught by Aungst et al. in view of Carson et al. Motivation is provided by Wills et al. by stating the p53 gene can be introduced into tumors to study the effect of p53 on tumor growth (page 1079, column 1, line 1). One of skill in the art would have had a reasonable expectation of success in administering a gene to a tumor cell

formulated in a buffer comprising BigCHAP or other surfactants. Because the applicants' claims as written are towards methods of treating disease, specifically bladder cancer, by administering a gene formulated in a buffer comprising a compound claimed wherein administration is by **any** route without causing **any** phenotypic change to the host, the cited prior art provides sufficient teachings and motivation to reach mere **delivery** of a gene.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

8. Claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) as applied to claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 above, and further in view of Takahashi et al. (1991, Proc. Natl. Acad. Sci. USA, Vol. 88, pages 5257-5261).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). It would have been obvious to one of skill at the time the invention was made to combine the surfactants of Aungst et al. with the method of delivering genes with detergents disclosed by Carson et al. Motivation is provided by Carson et al. by stating detergents which facilitate uptake of small molecules are well known in the art and may, without undue experimentation, be adapted for use in facilitating uptake of genes (column 8, line 59).

Aungst et al. in view of Carson et al. do not teach the delivery of a gene encoding full length retinoblastoma (RB) protein.

However, at the time of filing, Takahashi et al. disclose the delivery of a gene encoding full length RB protein into bladder carcinoma (page 5258, column 2, line 8 and line 16). It would have been obvious to one of skill in the art to combine the gene encoding full length RB protein of in bladder carcinoma by Takahashi et al. with the method of delivering a gene with surfactants as taught by Aungst et al. in view of Carson et al. Motivation is provided by Takahashi et al. by stating delivery and expression of RB using this construct can be used to analyze the effects of various growth factors and cytokines on signaling pathways in which RB is involved (page 5261, sentence bridging columns 1 and 2). Because the applicants' claims as written are towards methods of treating disease, specifically bladder cancer, by administering a gene formulated in a buffer comprising a compound claimed wherein administration is by **any** route without causing **any** phenotypic change to the host, the cited prior art provides sufficient teachings and motivation to reach mere **delivery** of a gene.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 21-22, 35-36 and 43-44 and 46-51 are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson
September 28, 1998

Deborah Crouch
DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630